REMARKS

Claims 147, 150-153, 155-156, 165, 168, 171-174, 176-177, 186, 189, 192-195, 197-198, and 207 have been canceled. Claims 166, 187 and 208 have been amended to correct a typographical error. No new matter has been added by way of amendment. Claims 158, 160-163, 166, 179, 181-184, 187, 200, 202-205, and 208 will be pending upon entry of the instant amendment.

Applicants appreciate the confirmation by telephone of the non-finality of the current Office action, as confirmed by Examiner Turner on May 4, 2006.

Election/Restrictions

Applicants appreciate withdrawal of the species election with respect to a single species of chemokine.

Double Patenting

Claims 147, 150-153, 155-156, 158, 160-163, 165-166, 168, 171-174, 176-177, 179, 181-184, 186-187, 189, 192-195, 197-198, 200, 202-205, and 207-208 were rejected by the Examiner under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 6,528,625. Specifically, the Examiner argued that the "instant claims are rendered obvious in view of the '625 patented claims directed to HB-12366 (2D7) antibody, antigen binding fragment, antibody producing hybridoma, compositions and test kit with properties including all limitations as instantly recited."

As stated in the response of November 28, 2005, Applicants will file a Terminal Disclaimer to overcome the Examiner's obviousness-type double patenting rejection as appropriate upon notice of otherwise allowable subject matter in the present application. This will permit Applicants to assess the appropriateness of the rejection in view of the claims as ultimately indicated to be allowable, since it is possible that the claims may change during the course of prosecution.

Supplemental Information Disclosure Statement

Applicants submit herewith a Supplemental Information Disclosure Statement including Lopalco et al. (Citation no. BT) and Roschke et al. (Citation number BU), cited below, as well as a number of U.S. Patents issued which correspond to PCT applications cited previously in the Information Disclosure Statements filed on October 2, 2001 and April 18, 2002.

Priority

Applicants note that the Examiner has given all pending claims the priority date of July 11, 1997.

The Rejection of Claims under 35 USC §103(a) Should Be Withdrawn

Claims 147, 150-153, 155-156, 158, 160-163, 165-166, 168, 171-174, 176-177, 179, 181-184, 186-187, 189, 192-195, 197-198, 200, 202-205, 207-208 were rejected under 35 USC §103(a) as being unpatentable over Li et al. (U.S. Patent Nos. 6,025,154 and 6,759,519), Raport et al., Combadiere et al., and Samson et al. (1996) as evidenced by Wu et al., Atchison et al, and Samson et al. (1997).

The Examiner argued that Li et al. "teach an antibody to human HDGNR10... HDGNR10 is the same protein as human CCR5," and stated that Li et al. "teach that the antibody may be a monoclonal, chimeric, single chain, humanized or human antibody, or fragments there of..." as well as compositions and kits comprising said antibodies. The Examiner asserted that Li et al. teaches "assays for screening for antagonists of both ligand binding and receptor function associated with that binding" and that Li et al. "also clearly contemplate that an antibody to CCR5 was such an antagonist and could be produced and identified by the appropriate screen..." However, the Examiner notes that Li et al. is "silent as to the preferred chemokine ligands that bind the receptor".

The Examiner cites three additional primary references — Samson et al. (1996), Combadiere et al., and Raport et al., stating that they "each teach ligand binding to CCR5 amongst ligands MIP-1α, MIP-1β, and RANTES and note that binding stimulates receptor function..." The Examiner additionally asserted that,

> "Raport et al. (AW) also notes that, 'this same combination of chemokines has recently been shown to potently inhibit human immunodeficiency virus replication in human peripheral blood leukocytes,' see in particular abstract noting others with direction to the N-terminus and second extracellular loop as important in mediating HIV infection." (emphasis added)

The Examiner reasoned that "while the cumulative references are silent to the fact that the ligand binding of MIP-1 alpha, beta and RANTES occurs at the second extracellular loop and that this specificity provides for the property of inhibition of HIV infection/entry, such properties are evidenced to map to the second extracellular loop. Therefore a screen as in Li for inhibition of ligand binding and receptor function would necessarily result in the selection of antibodies specific to the second extracellular loop." (emphasis added)

Finally, the Examiner argued that,

> "the art of record supports the conclusion that antibodies specific for inhibition of ligand binding and receptor function would be specific to the second extracellular loop and would also inhibit HIV binding/entry.
>
> Accordingly, the screening assay of Li when practiced with MIP-1alpha, beta and RANTES ligands as suggested by Samson (AV), Combadiere (AT3) and Raport (AW) would necessarily result in the identification of antibodies specific to the second extracellular loop, i.e. the chemokine binding and signaling site. That this site is also evidenced as the major co-receptor allowing infection of HIV is further evidenced as noted via Samson 1997 and Atchison AZ5. Hence, the screening assay of Li would identify antibodies capable of inhibiting infection of HIV as the ligand binding site of the second extracellular loop is critical to HIV infection. Both properties are evidenced as mapping to the same site, i.e. within the second extracellular loop." (emphasis added)

Applicants respectfully disagree and submit that the claimed invention is non-obvious over Li et al. (U.S. Patent Nos. 6,025,154 and 6,759,519), Raport et al., Combadiere et al., and Samson et al. (1996). As a preliminary matter, in an effort to expedite prosecution, Applicants have canceled claims 147, 150-153, 155-156, 165, 168, 171-174, 176-177, 186, 189, 192-195, 197-198, and 207. The remaining claims all include the limitation, "wherein said antibody or antigen binding fragment thereof additionally inhibits HIV infection".

Applicants agree that Li et al. teaches a human HDGNR10 that is the same as human CCR5. However, while Li et al. suggests making antibodies, they do not present any working examples of antibodies to CCR5. Neither does Li et al. teach or suggest any ligand(s) to CCR5, nor make any mention of the second extracellular loop or any HIV binding region of CCR5. Also, Applicants respectfully submit that even assuming *arguendo* that Li et al. did "contemplate" that "an antibody to CCR5 was such an antagonist and could be produced and identified by the appropriate screen", that such contemplation does not rise to the level of teaching or suggesting all of the claimed limitations so as to render the claimed invention obvious.

The Examiner points to the further primary references Raport et al., Combadiere et al., and Samson et al. (1996) for providing the ligands to CCR5. Raport et al., Combadiere et al., and Samson et al. (1996) are all CCR5 cloning papers identifying MIP-1α, MIP-1β, and RANTES as ligands for CCR5. However, Applicants submit that none of Raport et al., Combadiere et al., and Samson et al. (1996) teaches or suggests any importance of the second extracellular loop of CCR5 in any role.

In addition, Applicants respectfully submit that the Examiner's assertion that

> "Raport et al. (AW) also notes that, 'this same combination of chemokines has recently been shown to potently inhibit human immunodeficiency virus replication in human peripheral blood leukocytes,' see in particular abstract noting others with direction to the N-terminus and second extracellular loop as important in mediating HIV infection." (emphasis added),

is incorrect with respect to the location on CCR5 of HIV binding. Applicants respectfully note that Raport et al. is silent, in the abstract and throughout, with respect to portions of CCR5 important in mediating HIV infection. While Raport et al. cites a reference that investigated the effect of MIP-1α, MIP-1β, and RANTES on HIV infection, it makes no teaching, suggestion or reference to work by others as to which portions of CCR5 are involved in ligand or HIV binding.

The Examiner asserts a number of times that a screen to identify antibodies which inhibit ligand binding to CCR5 would necessarily identify antibodies that bind to the second extracellular loop and inhibit HIV infection, and that both such characteristics are evidenced as mapping to the same site, and therefore must be features of all antibodies to CCR5 that bind to the second extracellular loop and/or inhibit ligand binding.

Thus, the Examiner apparently argues that antibodies which would be determined to inhibit ligand binding would necessarily inhibit HIV infection. Applicants respectfully submit that the Examiner's argument is flawed. The fact that chemokines block HIV infection does not mean that HIV and chemokine ligands of CCR5 bind to the same place on CCR5, nor would one skilled in the art expect this to be the case. In fact, as Applicants point out below, Wu et al. and Atchison et al., for example, teach that HIV can bind to CCR5 in multiple places other than the second extracellular loop. Furthermore, the studies of Lopalco et al. (Journal of Immunology, 164:3426-3433, 2000, submitted herewith as Supplemental Information Disclosure Statement citation no. BT) demonstrate that anti-CCR5 antibodies found *in vivo* in the sera of HIV-exposed but seronegative individuals were "highly selective" for a first extracellular loop epitope, as no binding was observed on a "panel of synthetic peptides covering the complete sequence of the extra membrane region of CCR5," (emphasis added; see *e.g.* page 3431, section entitled "Epitope mapping of anti-CCR5 mAbs", Table I, and Figure 7).

The Examiner relies on three secondary references, namely Wu et al., Atchison et al, and Samson et al. (1997), as evidence that the claimed antibodies would necessarily be identified by a screen for antagonists to CCR5 ligand binding according to Li et al. Applicants respectfully disagree.

Wu et al. studied a panel of anti-CCR5 antibodies for ability to inhibit either chemokine binding or HIV-1 gp120 binding and HIV-1 infection. Using chimeric CCR2b/CCR5 receptors, Wu et al. mapped the domains on CCR5 recognized by these mAbs and correlated inhibitory activity with domain specificity of the mAbs. Wu et al. discloses that "efficient inhibition of an M-tropic HIV-1-derived envelope glycoprotein gp120 binding to CCR5 could be achieved with mAbs recognizing **either** the

second extracellular loop or the NH_2-terminal region." (emphasis added, see Wu et al., abstract). Thus, Applicants submit that the teachings of Wu et al. highlight the diversity of anti-CCR5 antibodies capable of inhibiting HIV infectivity. For example, Wu et al. discloses the antibody termed 3A9, which reacted only with chimeras that contained the NH_2-terminal region of CCR5, and that this 3A9 antibody exhibited significant inhibition of ^{125}I-gp120 binding (please see page 1375, paragraph spanning both columns; pages 1377-1378 and Figure 6A).

The Examiner also asserts that Samson et al. (1997) and Atchison et al. provide evidence that the chemokine binding site is also the site of HIV binding, and that the second extracellular loop of CCR5 is critical to HIV infection. With regard to Samson et al. (1997), Applicants respectfully submit that the only teachings in Samson et al. (1997) with respect to CCR5 and HIV infection are that the N-terminus and first extracellular loop of CCR5 are important in HIV binding/infection (please see page 23934, second column, first full paragraph) and that "regions of CCR5 involved in chemokine ligand specificity, and in the specificity of cofactor usage for various HIV-1 strains are not identical," (see page 24940, paragraph spanning first and second columns). Regarding Atchison et al., Applicants also submit that, contrary to the Examiner's assertion, Atchison et al. does not teach or suggest that the second extracellular loop of CCR5 is important for HIV infection. In fact, Atchison et al., at page 1925, first column, states that receptor chimeras containing the second extracellular loop of CCR5 "repeatedly had no coreceptor function" for HIV infection and that "substitution of the NH2-terminal segment from CCR5 (5222) conferred robust susceptibility to HIV-1 cell entry" (emphasis added). Furthermore, Atchison et al. state, "viral coreceptor activity is dissociable from ligand dependent responses". Thus, Samson et al (1997) teaches away from the second extracellular loop as important in HIV binding, and Atchison et al. also teaches away from the second extracellular loop for mediating HIV infection. Furthermore, neither Raport et al. nor Combadiere et al. teach, suggest, or even mention the second extracellular loop of CCR5 with respect to HIV binding/entry, and so cannot provide evidence that ligand binding and HIV binding map to the same site.

With respect to the Examiner's assertion that antibodies specific for inhibition of ligand binding would be specific to the second extracellular loop and would necessarily also inhibit HIV binding/entry, Applicants further submit that in fact, antibodies to CCR5 have now been reported which inhibit ligand binding to CCR5 but which do not inhibit HIV infection, demonstrating that inhibition of chemokine ligand binding does not necessarily equate to inhibition of HIV binding/entry. Applicants submit herewith reports by Roschke et al. ("Characterization of a Panel of Novel Human Monoclonal Antibodies that Antagonize CCR5 and Block HIV-1 Entry" 44th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 2004, Abstract #2871; submitted herewith as Supplemental IDS citation number BU) who studied anti-CCR5 antibodies and their ability to inhibit ligand binding and/or HIV infection.

Roschke et al. generated a large panel of monoclonal anti-CCR5 antibodies and examined the ability of these antibodies to bind CCR5, inhibit MIP-1β binding to CCR5, and to inhibit HIV viral entry (please see abstract, results section, and Figure 1 or Roschke et al). Roschke et al. noted "interestingly, while the most potent inhibitors of HIV-1 infection were effective at blocking chemokine binding, the ability to block chemokine binding and to block HIV-1 infection were **not mutually inclusive** (Figure 1)". (emphasis added)

Importantly, Roschke et al. disclose at least four antibodies in Figure 1 which inhibit MIP-1β binding potently, but which do not inhibit HIV viral entry (Figure 1, especially CCR5mAbs 20, 33, 37 and 38). For example, CCR5mAbs 20, 33, 37 and 38 each have an IC_{50} for inhibiting MIP-1β binding which is similar to or lower than the antibody chosen for further focus, mAb004 (i.e. 0.80, 0.04, 0.50, and 0.50 nM versus 0.41 nM for mAb004) but do not inhibit HIV viral entry. Thus, the studies of Roschke et al. demonstrate that anti-CCR5 antibodies capable of inhibiting ligand binding are not necessarily capable of also inhibiting HIV infection. Therefore, contrary to the Examiner's assertion, antibodies identified by a screen suggested by Li et al., directed to identifying antibodies which inhibit chemokine ligand binding to CCR5, would not necessarily also have the characteristic of inhibiting HIV infection.

To summarize, Applicants submit that antibodies or antigen-binding fragments thereof which

1) bind to the second extracellular loop of a human CCR5,

2) inhibit binding of MIP-1α, MIP-1β, RANTES, or a combination thereof to the receptor, and

3) inhibit one or more functions associated with binding of the chemokine to the receptor,

do not necessarily have the ability to

4) additionally inhibit HIV infection.

Contrary to the Examiner's assertion, antibodies identified by a screen suggested by Li et al., directed to identifying antibodies which inhibit chemokine binding to CCR5, would not necessarily also have the characteristic of inhibiting HIV infection. The art cited by the Examiner is either silent in this respect or teaches away from such characteristics, and the studies of Roschke et al. provide examples of antibodies which bind the second extracellular loop but do not inhibit HIV infection.

Applicants submit that Li et al., Raport et al., Combadiere et al., and Samson et al. (1996), do not teach or suggest all of the limitations of the instant claims, either alone or in combination, and Wu et al., Atchison et al, and Samson et al. (1997) either fail to demonstrate that the limitations are inherent in the primary references or actually teach away from such limitations. Thus, the cumulative reference teachings do not render the presently claimed invention obvious.

Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection of claims under 35 USC §103(a).

CONCLUSIONS

In view of the remarks and amendments made herein, Applicants respectfully submit that the objections and rejections presented by the Examiner are now overcome and that this application is in condition for allowance. If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

This paper is being filed timely as a request for two month extension is filed concurrently herewith. Applicants believe no further extensions of time are required. In the event any additional extensions of time are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

Entry of the remarks made herein is respectfully requested.

Respectfully submitted,

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